Clinical Risk Following Abrupt and Gradual Withdrawal of Maintenance Neuroleptic Treatment

Adele C. Viguera, MD; Ross J. Baldessarini, MD; James D. Hegarty, MD, MPH; Daniel P. van Kammen, MD, PhD; Mauricio Tohen, MD, DrPH

Background: Abrupt discontinuation of long-term psychotrophic medication can be followed by a high risk of early relapse. This study aimed to quantify the relapse risk over time in patients with schizophrenia following discontinuation of maintenance neuroleptic treatment.

Methods: Data on the timing of relapses in patients with schizophrenia after withdrawal from neuroleptic therapy were located by a computerized literature search, combined with new data, and evaluated by survival analysis.

Results: Data were found for 1210 schizophrenic subjects: 1006 (795 inpatients and 211 outpatients) were withdrawn abruptly from oral neuroleptic therapy, and 204 discontinued treatment gradually (≥3 weeks) or stopped treatment with depot neuroleptic drugs. After abrupt discontinuation of oral medication, the risk of relapse reached 50% within 30 weeks, with remarkably little additional risk thereafter to 3.7 years; inpatients relapsed more rapidly than did outpatients (10 vs 18 weeks to a 25% relapse risk). In studies including subjects whose drug therapy was withdrawn abruptly (n = 49) vs gradually (n = 58), relapse was earlier after abrupt discontinuation (25% risk in 6 vs 10 weeks), with a persistent difference for at least 6 months.

Conclusions: The relapse risk was high within 6 months of discontinuing oral neuroleptic therapy, particularly in hospitalized patients. Most patients who remained stable for 6 months continued to do so for long periods without medication, indicating clinical heterogeneity. Drug-withdrawal stressors, related to long-term pharmacodynamic adaptations, are implicated. Since the risk was lower after gradually discontinuing oral neuroleptic therapy or stopping depot injections, early relapse may be spared by a slow removal of drugs.

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Following their introduction in the 1950s, neuroleptic drugs became the cornerstone of pharmacological treatment of psychotic disorders. The findings from many studies support their short-term efficacy and long-term benefits.

Most studies of neuroleptic maintenance have involved the interruption of treatment to compare a placebo with continued medication. Meta-analyses of such studies have found high rates of relapse in the weeks after the interruption of active treatment. Gilbert and colleagues recently concluded that the risk of psychotic relapse within 10 months was only 16% if antipsychotic medication was continued, and 53% after discontinuation.

Late adverse effects (particularly tardive dyskinesia) encourage attempts to minimize the risks without a loss of the benefits of maintenance neuroleptic therapy. Options include individual adjustment to a minimum effective dose, as well as the use of very low or intermittent dosing. Low or intermittent dosing involves the removal of neuroleptic drugs. Such procedures and, indeed, the research that supports long-term neuroleptic treatment, evidently assume that the removal of a drug does not increase the clinical risk above that associated with the natural history of untreated illness. Critical reevaluation of this assumption is encouraged by a recent
MATERIALS AND METHODS

We searched for studies that involved the abrupt or gradual discontinuation of maintenance treatment with oral antipsychotic agents or stopping injections of long-acting preparations in patients who were diagnosed as having schizophrenia. MEDLINE-computerized searching and references obtained from the resulting reports yielded 11 studies with data on the time to relapse for individuals, or survival analyses of groups, and provided 1006 subjects (795 inpatients and 211 outpatients) who were abruptly withdrawn from oral neuroleptic maintenance.25-29 Similar new data involved 94 subjects with schizophrenia according to DSM-III-R criteria who were rapidly discontinued from oral haloperidol at the Highland Drive Veterans Affairs Medical Center, Pittsburgh, Pa (methodological details have been reported elsewhere6,7,30) and 6 similar subjects from a study at the Massachusetts Mental Health Center, Boston, on removing an average of 85% of the initial medication (A. I. Green, MD, S. V. Farbman, PhD, W. A. Brown, MD, J. Gutierrez, MD, and M. T. Tsuang, MD, DSc, PhD, oral and written communications [generously provided by Dr Green to R.J.B.], June 1995). Four studies (n=107 subjects, including 7 from Dr Green) provided additional data on gradual (>3 weeks) withdrawal of oral medication.31,32,34,35 Five studies (n=85 cases, including 8 from Dr Green) involved stopping injections of a long-acting neuroleptic drug.35,36-39 We excluded several studies that involved simultaneous or undefined mixtures of oral and depot neuroleptic medications, intermittent neuroleptic therapy, or imprecisely defined timing of drug discontinuation. Analyses are based on findings from 16 reports plus 2 unpublished data sets, yielding 1210 patients who were diagnosed as having schizophrenia and followed up after discontinuation of maintenance neuroleptic treatment.25-29 Characteristics of the 22 cohorts that were studied25-29 are summarized (Table 1); some studies failed to specify drugs and doses but did indicate when oral or depot medication was involved. Definitions of relapse or exacerbation of illness varied but usually involved clinical assessment or the use of rating scale scores to indicate the worsening or psychotic symptoms severe enough to warrant hospitalization or reinstitution of antipsychotic treatment. Discontinuation and follow-up assessments were double-blind in 20 of the 22 cohorts (only 2 studies were open). “Abrupt” discontinuation usually involved stopping neuroleptic treatment within 1 day; “gradual” discontinuation included the tapering of oral doses over at least 3 weeks (mean±SD, 3.39±6.00 months), or no further depot neuroleptic therapy after a final injection. Treatment averaged 7.75±6.07 months and postwithdrawal follow-up after the last dose averaged 54±46 weeks (range, 10 weeks to 4 years), or 16, 20, and 17 months after discontinuing oral medication treatment abruptly or gradually, or stopping depot injections, respectively (Table 1).

The relapse risk over time after the discontinuation of neuroleptic therapy was analyzed by Kaplan-Meier and actuarial survival analysis, with variances, and compared statistically by Mantel-Cox nonparametric log rank techniques to provide a x².20,23,35 These values, as well as the time to a defined percent relapse±SE, were calculated with commercially available microcomputer programs (Statview/Survival Tools, Abacus Concepts, Inc, Berkeley, Calif). Unless otherwise stated, data are presented as the median SD or rates±SE, 2-tailed statistical significance required P<.05 (nonsignificance, P=.10).

RESULTS

The survival function after abrupt discontinuation of oral neuroleptic treatment in 1066 schizophrenic patients (Figure 1) indicated a rapid failure of clinical stability within 3 to 6 months, reaching a relapse risk of 25% within

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Table 1

<table>
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<tbody>
<tr>
<td>Setting</td>
<td>1. Inpatient, 2. Outpatient</td>
<td>1. Inpatient, 2. Outpatient</td>
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<tr>
<td>Follow-up</td>
<td>1. 3 months, 2. 6 months</td>
<td>1. 3 months, 2. 6 months</td>
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ences between hospitalized and ambulatory patients were similar when those who were undergoing gradual removal of neuroleptic drugs were included (data not shown). The survival over time was very similar after the gradual discontinuation of oral medication over an average of 3.39±6.39 months and stopping depot injections (n=113 and n=91, respectively; $X^2=0.12; P>.10$), thus, the data were pooled to provide a group of patients with gradual discontinuation of treatment. There was no significant overall difference in the resulting survival functions for those who discontinued treatment abruptly vs gradually (n= 1006 and n=204, respectively; $X^2=1.05; P>.10$), although the time to a 25% relapse risk tended to be shorter after abrupt discontinuation (11.0±0.3 vs 15.0±1.0 weeks).

Table 1. Analysis of Schizophrenia Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>% Mortality</th>
<th>Diagnosis</th>
<th>Agents Discontinued</th>
<th>Mean Treatment Prior to Discontinuation</th>
<th>Relapse Follow-Up</th>
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</thead>
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<tr>
<td>Olson and Peterson, 1980</td>
<td>117</td>
<td>4.3</td>
<td>Oral</td>
<td>Depot</td>
<td>1.75±6.01 months</td>
<td>Gradual 420 days (3.39±6.39 months)</td>
</tr>
<tr>
<td>Winterer and Hoy, 1983</td>
<td>19</td>
<td>5.3</td>
<td>Oral</td>
<td>Depot</td>
<td>1.75±6.01 months</td>
<td>Gradual 23 days (3.39±6.39 months)</td>
</tr>
<tr>
<td>Miller et al., 1985</td>
<td>12</td>
<td>8.3</td>
<td>Oral</td>
<td>Depot</td>
<td>1.75±6.01 months</td>
<td>Gradual 30 days (3.39±6.39 months)</td>
</tr>
<tr>
<td>Greenberg and Rose, 1986</td>
<td>15</td>
<td>6.7</td>
<td>Oral</td>
<td>Depot</td>
<td>1.75±6.01 months</td>
<td>Gradual 60 days (3.39±6.39 months)</td>
</tr>
<tr>
<td>Erhardt et al., 1987</td>
<td>41</td>
<td>7.3</td>
<td>Oral</td>
<td>Depot</td>
<td>1.75±6.01 months</td>
<td>Oral 10.2±0.6 weeks, 50% within 30.3±15.4 weeks; Depot 25% within 18.0±1.65 weeks, 50% within 3.69 years of follow-up</td>
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*These studies of cohorts for which neuroleptic maintenance treatment was discontinued involved 1210 psychotic inpatients or outpatients who were receiving long-term maintenance neuroleptic treatment in clinically stable status prior to discontinuation; diagnoses were based on unspecified clinical criteria, Research Diagnostic Criteria (RDC), or the American Psychiatric Association DSM-III or DSM-III-R. 
†Gender was defined as the percentage of men; (50%) indicates approximately equal numbers of men and women subjects; approximately 69% were men. 
‡Settings of studies were inpatient (I) units (41%) or outpatient (O) clinics (53%). 
§Depot esters (decanoate and palmitate) were injected intramuscularly.

Oral neuroleptic drugs were removed rapidly in 795 inpatients and 211 outpatients. Their stability after drug removal differed markedly (Mantel-Cox $X^2=28.4; P<0.001$ [Figure 2]): 25% of inpatients vs outpatients relapsed within 10.0±0.62 vs 18.0±1.65 weeks, and 50% of inpatients relapsed within 18.0±1.65 weeks, while only 40.8% of outpatients relapsed within a maximum of 3.69 years of follow-up (Figure 2). Within 6 months without medication, the relapse risk (±SE) was 49.6%±1.8% for inpatients vs 31.4%±3.2% for outpatients. Differences between hospitalized and ambulatory patients were similar when those who were undergoing gradual removal of neuroleptic drugs were included (data not shown). The survival over time was very similar after the gradual discontinuation of oral medication over an average of 3.39±6.39 months and stopping depot injections (n=113 and n=91, respectively; $X^2=0.12; P>.10$); thus, the data were pooled to provide a group of patients with gradual discontinuation of treatment. There was no significant overall difference in the resulting survival functions for those who discontinued treatment abruptly vs gradually (n=1006 and n=204, respectively; $X^2=1.05; P>.10$), although the time to a 25% relapse risk tended to be shorter after abrupt discontinuation (11.0±0.3 vs 15.0±1.0 weeks).
The present findings from 1960 to 1995 should be interpreted cautiously owing to the variability in diagnostic criteria, lengths and methods of follow-up, and definitions of relapse, as well as the types, duration, and doses of neuroleptic drugs (Table 1). Most reports also provided little information about possibly relevant aspects of clinical history, current state, and nonpharmacological variables in aftercare. Since most data were derived from the randomized placebo cohorts of controlled trials, following substantial periods of stabilization with drug treatment, it is probable that acutely ill patients were excluded from drug withdrawal. Despite these caveats, the present analyses yield interesting information about the relapse risk over time, especially its relation to hospitalization and to the rate of drug removal.

There was a high early risk of exacerbation of psychotic symptoms soon after the abrupt interruption of ongoing oral neuroleptic maintenance. The initial relapse rate was after the abrupt therapy, and abrupt discontinuation (Table 1, Table 2) of the oral neuroleptic drugs, the likelihood of relapse (Figure 1) was greater for patients who were abruptly withdrawn from neuroleptic therapy. The risk was greater for patients who were withdrawn abruptly (χ²= 11.1; P < .001), of whom 50% relapsed within 2.5 months; patients followed up to 4 years without reaching a 50% relapse risk (data not shown).

COMMENT

The present findings from 1960 to 1995 should be interpreted cautiously owing to the variability in diagnostic criteria, lengths and methods of follow-up, and definitions of relapse, as well as the types, duration, and doses of neuroleptic drugs (Table 1). Most reports also provided little information about possibly relevant aspects of clinical history, current state, and nonpharmacological variables in aftercare. Since most data were derived from the randomized placebo cohorts of controlled trials, following substantial periods of stabilization with drug treatment, it is probable that acutely ill patients were excluded from drug withdrawal. Despite these caveats, the present analyses yield interesting information about the relapse risk over time, especially its relation to hospitalization and to the rate of drug removal.

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symptomatic differences between hospitalized and ambulatory psychotic patients.1,5,7

The full implications of the present findings are limited by the typically complex and irregular course of untreated schizophrenic 46-67 to be compared with the course following discontinuation of treatment. Although clinical and possible ethical considerations now severely constrain observations of untreated psychotic patients for prolonged periods,13,14 treatment noncompliance as well as elective clinical practice often interrupt antipsychotic treatment for varying periods. In psychotic affective disorders, intermittent-interrupted exposure to neuroleptic drugs is particularly common, and its potential contribution to clinical instability is unknown.1,2,5,5 In addition, most experimental protocols that evaluate the long-term efficacy of neuroleptic agents and many other drugs have compared continued vs withdrawn treatment.3,15-17 The results of such studies that support a therapeutic effect usually have not considered contributions of drug withdrawal to observed drug-placebo contrasts. Moreover, protocols that have been designed to study patients in a presumed drug-free state often have employed a drug "washout" that was probably too short to provide a drug-free and physiologically basal state.1,2,5,4

In conclusion, rapid discontinuation of maintenance treatment with short-acting oral neuroleptic agents in schizophrenia carried a 50% risk of relapse within 30 weeks; pharmacodynamic stress factors contributing to this risk may include supersensitivity of central dopamine receptors. Further study is required to clarify whether (1) the high morbidity following abrupt interruption of maintenance treatment exceeds that in untreated psychotic illness and (2) gradual drug removal can reduce, and not merely postpone, relapse. In general, the present findings add to growing evidence that abrupt discontinuation of maintenance treatment with psychotropic agents is followed by a high rate of early relapses in several major psychiatric disorders: This phenomenon should be considered in the design and interpretation of research protocols as well as in clinical management; and the rates reported here should help in planning research and in counseling patients. Gradual dose reduction (with close clinical follow-up) may limit relapse risk associated with interruption of maintenance treatment, and is recommended.

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REFERENCES